84-2 - Chinese Hamster - Micronucleus Test (5-7-87)

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DATA EVALUATION REPORT

Study Type: Cytogenetic Analysis

TOX. CHEM. No.: 298C

Accession No.: 7E3489

MRID No.:

Test Material: CGA 154281 Technical (93.9% Purity)

Study Number(s): 860109

Sponsor: CIBA-GEIGY Corp.

Test Facility: Experimental Pathology Laboratories, CIBA-GEIGY Limited
Basal, Switzerland

Title of Report:
Micronucleus Test (Chinese Hamster)

Author(s): F. Strasser, H. Loos, M. Langauer and L. Loos

Report Issued: November 3, 1986

Conclusions:

Under the test conditions reported, CGA 154281 Technical is not clastogenic in the Chinese Hamster Micronucleus Test at the dose levels tested.

Dose Levels tested: 1250, 2500, and 5000 mg/kg

Classification of Data: Unacceptable

PC [illegible]

Title of Report: Chinese Hamster Micronucleus Test with CGA 154281 Technical

Procedure:

1. Test Animals:

Chinese hamsters (Cricetulus griseus) of both sexes (females, 6-10 weeks old; males, 4-9 weeks old) were used in this study. The animals were acclimated to laboratory conditions for 5 days prior to initiation of the study and were housed in an environmentally controlled room with food (NAFAG No. 924) and water available ad libitum.

2. Route of Administration:

CGA 154281 Technical was administered by gavage. In the first part of this study, the animals were treated once with the highest applicable dose of 5000 mg/kg and sacrificed 16, 24, and 48 hours thereafter. In the second part of this study, the animals were treated once with the doses of 1250, 2500, and 5000 mg/kg and sacrificed 24 hours thereafter.

Following were the groups designation and the distribution of animals among the groups:

Group	Number Males	Hours Sacrificed	Number Females	Hours Sacrificed	Dosage Level
1st Study:					
Solvent Control	3	(16)	7	(16)	0.5% CMC
	10	(24)	10	(24)	"
	5	(48)	5	(48)	"
Positive Control	5	(24)	5	(24)	CCPM
CGA 154281	3	(16)	7	(16)	5000 mg/kg
(High Dose)	5	(24)	5	(24)	"
	5	(48)	5	(48)	"
2nd Study:					
Solvent Control	5	(24)	5	(24)	0.5% CMC
Positive Control	5	(24)	5	(24)	CCPM
CGA 154281 - Low	5	(24)	5	(24)	1250 mg/kg
" - Mid	5	(24)	5	(24)	2500 "
" - High	5	(24)	5	(24)	5000 "

Dosing Factor = 20 ml/kg for all groups.

3. Preparation of Bone Marrow:

Bone marrow was harvested from the shafts of both femurs with fetal calf serum. After centrifugation, small drops of the sediment mixture were transferred on the end of slide, spread out with the aid of a glass slide

and the preparations were air-dried. Within 24 hours, the slides were stained in undiluted May-Grunwald solution. After being rinsed in distilled water, the slides were left immursed in diluted Giemsa solution (16.6%) for 10 minutes and rinsed again with distilled water.

4. Scoring of the Slides

One thousand polychromatic erythrocytes were examined from each animal and the following information was recorded: The number of Polychromatic erythrocytes; The number of normochromatic erythrocytes; The ratio of polychromatic to normochromatic erythrocytes; The number of polychromatic erythrocytes with micronuclei; The percent of polychromatic erythrocytes with micronuclei.

5. Statistics

The significance of difference was assessed by X^2 - test.

Results:

Micronucleus Test in Chinese hamsters

Treatment	Sampling Time (Hrs)	No.of PCEs Analyzed Per Group	No.of NCEs Analyzed Per Group	Ratio Of PCE to NCE	No. of PCEs with Micronuclei	Percent Micro-nuclei/ Group	P Value
1st Trial:							
Solvent Control	16	5113	4887	1.05	5	0.097	-
CGA 154281							
5000 mg/kg	16	4461	5539	0.81	6	0.13	NS
Solvent Control	24	4358	5642	0.77	4	0.092	-
CGA 154281							
5000 mg/kg	24	4437	5563	0.80	4	0.09	NS
Solvent Control	24	4358	5642	0.77	4	0.091	-
Positive Control							
(CCPM, 64 mg/kg)	24	3461	6539	0.53	457*	1.32*	P<0.05
Solvent Control	48	5428	4572	1.19	7	0.13	-
CGA 154281							
5000 mg/kg	48	4423	5777	0.77	6	0.14	NS
2nd Trial:							
Solvent Control	24	4520	5480	0.82	5	0.11	-
Positive Control							
(CCMP. 64 mg/kg)	24	3686	6314	0.58	179*	0.48*	P<0.05
CGA 154281							
1250 mg/kg	24	3979	6021	0.66	1	0.03	NS
2500 "	24	4207	5793	0.73	3	0.07	NS
5000 "	24	3964	6036	0.66	5	0.13	NS

* Siginificant increase over the control value P<0.05; Solvent control = 0.5% CMC; CCPM = Cyclophosphamide; NS = Not Significant.

Results: continued

Findings:

1. From the results of the preliminary toxicity test for this compound, the dose of 5000 mg/kg was determined as the highest applicable dose in this study.

2. The spontaneous rate of micronuclei in the polychromatic erythrocytes found from the solvent control groups was within the normal range (i.e., 0.09 to 0.13%).

3. The positive control compound, Cyclophosphamide, apparently induced significant increase of the PCE containing micronuclei ($P<0.05$) which indicated the sensitivity of the assay system.

4. The test compound, CGA 154281 Technical, did not induce any significant increase of the PCE containing micronuclei from the treated animal groups when compared to that of the solvent control group at all three sampling times.

Evaluation:

The assay procedure used in this study appears to follow the general procedure of micronucleus test for cytogenetic analysis described by Schmid (1976). However, the following inadequacies in reporting of this study must be corrected:

1. Althogh the preliminary toxicity test for dose selection was briefly described in this report, the toxic index of the test compound was not given. The reliable index for the toxic effect of the test compound in this assay system should be based on the PCE:NCE ratio. The maximum tolerated dose selected for this study should demonstrate toxicity in nucleated stem cells which was recognized by lower proportion of polychromatic erythrocytes and higher proportion of normochromatic erythrocytes filling the marrow cavity.

2. Individual clinical observations and individual body weight measurement on the test animals following treatment were not presented in this report.

Since the submitted report is inconclusive, the study is unacceptable in the present form. However, the study may be upgraded on resolution of the reporting deficiencies.